REMARKS

Concerning the Examiner's rejection of the pending claims on the ground of a non-statutory obviousness type double patenting over US Patent No. 6,489,467 please consider the following.

The present invention as claimed in claim 1 is directed to a process for preparing sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration, comprising the steps of providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration; passing said aqueous formulation through a filter having a pore size of less than 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and after the concentration step filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use.

To the contrary, US 6,489,467 claims a process for purifying HA powder, which process involves the steps of diafiltration (step a) and the removing of cells (step b) from an aqueous solution of hyaluronic acid obtained from a biological source, followed by subsequently sterilizing the thus purified HA containing solution (step c). In the method of US 6,489,467, the sterilization step is carried out by passing the purified HA containing solution through a 0.2 μm filter (col.6 lines 9-23, col.7 lines 51-54, col.8 lines 63-67, claims 8, 19, 27). According to US 6,489,467, the solution thus obtained may then be freeze dried to obtain a dry powder of purified HA. It is described in US 6,489,467 (see col. 6 lines 27-32) that after the sterilization step the solution may be pre-concentrated by filtration through a filter of pore size 5'000 – 10'000

Daltons nominal molecular weight cut off before freeze drying to obtain a dry powder of HA. This concentration by filtration is carried out solely to permit the subsequent freeze drying of the HA to obtain a dry HA powder. Concentration by filtration as taught by US 6,489,467 produces a wet HA containing residue suitable for freeze drying to obtain the purified HA dried powder. The concentration by filtration described in US 6,489,467 is not intended for and cannot be used for providing a concentrated aqueous solution of HA at a specified concentration of HA.

US 6,489,467 does not disclose, or make obvious in any way, the process for preparing a sterile, ready-to-use aqueous pharmaceutical formulation of HA at a specified concentration involving the specific combination of steps of providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration; passing said aqueous formulation through a filter having a pore size of less than 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and wherein after the concentration step, the pharmaceutical formulation is filled directly into sterile recipients ready for pharmaceutical use.

It is further be highlighted that US 6,489,467 teaches a method of preparing purified hyaluronic acid, in the form of a dry powder, which can then be used for the preparation of pharmaceutical compositions in a conventional manner (reference may be made to, for example, col. 7 lines 55-57 and col. 8 lines 3-5). The skilled person reading US 6,489,467 is, accordingly, taught a method for arriving at pharmaceutical formulations of HA, starting from dry purified HA powder, by conventional methods. The skilled person on reading US 6,489,467 has, accordingly, a method for arriving at pharmaceutical formulations of HA by conventional methods and has no reason whatsoever to look for any other method for preparing pharmaceutical formulations of HA. On the basis of the teaching of US 6,489,467 it is totally

unobvious for the skilled person to decide to stop following the method of US 6,489,467 after the step of sterilization by filtration, and then to instead subject this sterilized solution to a step of concentration under vacuum to a specific accurate pharmaceutical concentration, followed by filling directly into sterile recipients with the aim to provide an aqueous pharmaceutical formulation of high molecular weight HA ready for pharmaceutical use, as required by the present invention as claimed. It is clear that the Examiner's objection is entirely based on inappropriate hind-sight.

Concerning the Examiner's rejection on the pending claims on grounds of obviousness under 35 U.S.C. 103 (a) over WO 00/44925 in view of EP 0 631 799 A1, please consider the following.

WO 00/44925 is the International Application (No. PCT/IB00/00082) from which the cited patent US 6,489,467 was derived, and the description and examples of US 6,489,467 are identical with those of WO 00/44925.

Accordingly, WO 00/44925 is directed to a process for purifying high molecular weight hyaluronic acid, involving steps of diafiltration and removing of cells from an aqueous solution of hyaluronic acid obtained from a biological source, followed by sterilizing the obtained HA containing solution by passing a 0.2 μm filter. WO 00/44925 teaches that the filter sterilized HA containing aqueous solution may optionally be freeze dried to obtain a dry powder of HA in purified form (see for example page 10 last 5 lines of WO 00/44925 as published). WO 00/44925 teaches that the freeze dried dry powder of HA may subsequently "be used for preparing pharmaceutical compositions" (see for example page 13 paragraph 6 to page 14 first full paragraph, page 15 last two paragraphs to end of page 16).

Contrary to the Examiner's assertions on page 5 of the Office Action, the filtered solution obtained by the process of WO 00/44925 is not "ready for pharmaceutical use" as required by the claims of the present application. The HA containing solution obtained after the sterilization step (c) of the process of WO 00/44925 is not a pharmaceutical formulation ready for pharmaceutical use. The aqueous solution containing high molecular weight HA, obtained after steps (a) and (b), subjected to the described step of sterilization by filtration through a filter having a 0.2 μm pore size has necessarily a low concentration of hyaluronic acid not suitable for pharmaceutical application. At the concentrations of 1 to 3% HA required for high viscosity aqueous HA formulations for pharmaceutical use, not all of the HA would pass through a filter of 0.2μm pore size as taught for the sterilization step in WO 00/44925. This results in significant reduction in the concentration of HA and/or irreversible degradation of the high molecular weight HA, i.e. reduction of molecular weight of HA and reduction of viscosity, not acceptable for pharmaceutical applications (as described in the present application as filed page 4 last paragraph to page 5 fist paragraph).

According to WO 00/44925 the sterilized HA containing solution is freeze-dried to obtain a dry HA powder. WO 00/44925 teaches that the dry HA purified powder may subsequently be used for preparing pharmaceutical compositions. In other words, WO 00/44925 provides the skilled person with a method for purifying high molecular weight hyaluronic acid from a biological source and for preparing pharmaceutical formulations of this purified HA by conventional methods starting from the freeze-dried purified HA powder, i.e. by weighing out an accurate quantity of the dry HA powder and dissolving this in an accurate volume of water, with the addition of accurately measured quantities of desired excipients to provide an aqueous pharmaceutical formulation. The skilled person reading WO 00/44925 is thus taught how to go

about preparing a pharmaceutical formulation of HA and none of the cited prior art documents provide the skilled person with any reason to look for an alternative method for preparing sterile aqueous formulation of high molecular weight HA ready for pharmaceutical use. Since the skilled person is taught by WO 00/44925 to prepare pharmaceutical formulations from the freeze-dried powder of HA, it is totally unobvious from the teaching of the cited prior art for the skilled person to instead stop at the step (c) of sterilization of the purified HA of WO 00/44925 and, instead of following the teaching of WO 00/44925, on the contrary to concentrate the aqueous solution by applying a vacuum and boiling off water until a pre-specified accurate pharmaceutical concentration is reached; and then filling the formulation directly into sterile recipients with the aim to provide aqueous formulations of HA ready for pharmaceutical use, as required by present invention, as claimed.

The Examiner cites EP 0 631 799, which is directed to a vacuum concentrating plant in which a feed liquid is heated indirectly by a latent heat produced by introducing depressurized vapour into a steam jacket, with the aim of providing high heat efficiency. There is nothing whatsoever in EP 0 631 799 that provides any motivation to a skilled person to introduce the vacuum concentration process described therein into the purification process described in WO 00/44925 at any step in the process described therein, i.e. after any of the steps (a), (b), or (c), let alone to suggest to the skilled person any reason for wishing to apply the vacuum concentration method of EP 0 631 799 specifically to the sterilized solution produced after the filter sterilization step (c) of WO 00/44925.

Furthermore, even if the person skilled in the art were inventively to desire to apply the vacuum concentration process of EP 0 631 799 to the sterilized HA containing solution produced in step (c) of the process of WO 00/44925, he would not arrive at the present invention, as

claimed. EP 0 631 799 does not provide any teaching of the preparation of pharmaceutical formulations having an accurate, pre-determined, concentration. Indeed, EP 0 631 799 does not describe or suggest how any means for monitoring of the concentration of the liquid in the vacuum evaporator during the concentration process, or means for stopping the vacuum evaporation concentration process in the apparatus described therein abruptly when the desired concentration of substrate has been reached, could be integrated into the apparatus described in EP 0 631 799, or even whether it would be feasible to do so. Further, EP 0 631 799 does not provide any teaching whatsoever of the filling of a pharmaceutical formulation, having a specified pharmaceutical concentration of HA directly into sterile recipients ready for pharmaceutical use.

It may be further highlighted to the Examiner that the process of the present invention as claimed allows for the first time the preparation of sterile pharmaceutical formulations of high molecular weight HA ready for pharmaceutical use in which the required properties of high molecular weight of hyaluronic acid and determined high viscosity are maintained. No additional preparation steps are required before pharmaceutical use of the HA formulations prepared to the present invention. The process of the present invention avoids the need for additional manipulations of weighing out accurately specific amounts of sterilized concentrated sodium hyaluronic powder, mixing the powder with a defined precise volume of water and precise quantities of excipients, and the associated risks of contamination due to the removal of the sterilized HA powder from storage vessel, transfer to a measuring vessel and then transfer to a vessel in which the powder would be mixed with water, before finally being filled into recipients for pharmaceutical use; encountered in the preparation of pharmaceutical formulations by the conventional methods. In order to meet health authority standards for administration in the

human body, the aqueous formulations prepared from sterilized HA powder by prior art conventional methods must be subjected to further sterilization, such as by autoclaving of the formulation filled in vials or syringes before it may be used for pharmaceutical use. This is not necessary for the sterile ready for pharmaceutical use formulations of high molecular weight HA of the present invention.

Finally, with respect to the Examiner's comment on page 5 of the Office Action concerning claim 8 of the present application, whereby the Examiner asserts that WO 00/44925 "discloses a monitoring of optical density of the solution during filtration," it is respectively submitted that WO 00/44925 does not disclose the measurement of HA concentration with a spectrophotometer sensing wave radiation absorption in the formulation as required by claim 8 of the present application. To the contrary, WO 00/44925 describes in step (a) that in the purifying process that the visco-elastic aqueous solution/broth containing the high molecular weight hyaluronic acid is preferably diafiltered until the "filtrate which is disgarded as an optical density at a wave length of 280 nm equal or lower than 0.02" (page 7 last paragraph to page 8 first paragraph). What is described in WO 00/44925 is that the acidified HA containing broth from biological source is diafiltered on a filter having a pore size in the range 100'000 Daltons to 0.45 μm, whereby at the acidic pH of pH 1.7 to 3.3 a cross-linked network of HA molecules is formed which is retained on the filter, whereas proteins and other material impurities pass through the filter (i.e. separating the HA from soluble impurities contained in the solution) (see for example page 6 of WO 00/44925). Accordingly, in the cited passage at page 7 last paragraph to page 8 first paragraph, what is described is the measuring of the optical density of the filtrate of this diafiltration, after each diafiltration to measure the level of impurity in the filtrate, in order to determine when sufficient repeats of the diafiltration purification step have been effected.

There is no teaching whatsoever of the use of a spectrophotometer sensing wave radiation absorption to monitor HA concentration in-situ in a step of concentration of a solution of HA to a pre-determined specified concentration as required by claim 8.

For all of these foregoing reasons, reconsideration of the claims of the present application is respectfully requested, followed by allowance of claims 1, and 4-9, over all the prior art of record.

Respectfully submitted,

By: _____

Clifford W. Browning
Reg. No. 32,201
Krieg DeVault LLP
One Indiana Square
Suite 2800
Indianapolis, IN 46204
(317) 238-6203